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הום נמיים יוצרים ייצורים
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آن לעשות כל שימוק מסחרי במאמרים.
Naturally Occurring Chromium Compounds in Brewer’s Yeast and the Saltbush Plant

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The activity of glucose tolerance factor (GTF), an active organic chromium (Cr) compound, was measured in extracts from Brewer’s yeast and the saltbush plant (two natural sources known for their antidiabetic potential). GTF was found active both in vivo and in vitro. A dose-dependent increase in yeast fermentation was found. Maximal activity was reached with 10 ng Cr/ml in yeast extract and 150 ng Cr/ml in the saltbush preparation. In vivo studies were performed on streptozotocin-diabetic rats, a model for Type I diabetes, and on spayy mice and sand rats, models for type II diabetes. A single dose of GTF orally administered to streptozotocin-diabetic rats immediately reduced blood glucose and lipids, reaching a maximum within 2–3 hours. The rate of decrease in blood glucose was dose dependent—12% reduction after 3 hours for 70 ng Cr/animal and 22% reduction with 280 ng Cr/animal. The duration of the effect was also dose dependent: blood glucose levels of treated animals returned to initial values within 6 hours for 280 ng Cr/animal and 9 hours for 1,120 ng Cr/animal. GTF was found to potentiate insulin action: 23.5% decrease in blood glucose values occurred within 120 min for GTF administered alone (P < .001); 12.5% decrease for marginal insulin: 0.005–0.025 mg/Kg (P < .001), and 42% decrease for simultaneous administration of both agents (P < .001). Oral glucose tolerance tests on Type II diabetic animals showed a remarkable improvement in glucose tolerance following an oral dose of GTF. GTF preparations from Brewer’s yeast or saltbush have a remarkable effect on glucose metabolism both in vivo and in vivo. J. Trace Elem. Exp. Med. 12:111–124, 1999. © 1999 Wiley-Liss, Inc.

Key words: chromium; glucose tolerance; glucose tolerance factor (GTF); diabetes

INTRODUCTION

Chromium (Cr) has been known for more than three decades as an essential trace element needed for animal and human nutrition [1–4]. Rats fed a Cr-deficient diet developed glucose intolerance [5] in addition to elevated levels of blood glucose and cholesterol, decreased growth, and a reduced life span [6]. Serum and tissue Cr

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concentrations in old or diabetic animals are lower than in young and healthy animals [7,8]. Chromium is the only element known in humans to decline in most organs with age [7–10]. Its concentrations in diabetics are even lower than in other healthy adults [10].

Patients on long-term total parenteral nutrition developed severe symptoms of glucose intolerance, which could be partially reversed by intravenous administration of very high concentrations (150–250 μg Cr/day) of CrCl₃ [11]. Malnutrition associated with Cr deficiency also can bring on impaired glucose tolerance. Diabetic symptoms in malnourished children were reversed by a single dose of 250 μg Cr as CrCl₃ [12]. Inorganic Cr compounds are poorly absorbed by the gut [13], whereas organic Cr compounds are well absorbed in the body [14–16].

The glucose tolerance factor (GTF) is a dietary agent first isolated by Mertz and Schwarz [1] from Brewer’s yeast. This natural organic Cr compound reversed the impaired glucose tolerance of rats fed a diet of Torula yeast, which is known for its poor Cr concentration. Only a few studies were conducted with GTF (or Brewer’s yeast extracts high in GTF) on humans. Doisy [17] found an improvement in glucose tolerance in 50% of elderly patients with impaired glucose tolerance after 2 months of treatment. A significant improvement in glucose tolerance and blood lipid concentration was observed in other studies after administration of Cr-rich yeast extracts [16,18,19].

In vitro studies with partially purified preparations of GTF demonstrated stimulation of glucose metabolism in several tissues in the presence of insulin [20–22]. GTF has a low molecular weight, is soluble in water, and is readily absorbed by the gut. In addition to Cr, it probably contains nicotinic acid and three amino acids—glycine, cystein, and glutamic acid [3,4]. GTF can be extracted from several sources, including liver, black pepper, kidney, dairy products, broccoli, and barley [23,24]. The richest source for GTF is Brewer’s yeast [1–4,20,25]. In contrast to simple Cr salts that are poorly absorbed [26] and need a long period of time to achieve a partial improvement in glucose tolerance [2–4], natural GTF exhibits remarkable improvement in glucose tolerance in both diabetic animals and human subjects [27].

Despite the high importance of this natural existing active Cr compound, GTF has not been characterized or identified as yet. Several organic Cr compounds were proposed to serve as the GTF, among them the extract derived from yeast, according to a procedure developed by Mertz et al. [3,4,20]. This partially purified Cr compound is cationic, soluble in water, and shows absorption at 260 nm. In vitro studies with this preparation showed high biological activity in glucose transport into yeast cells [28], adipocytes [22], and cardiomyocytes [29]. A remarkable effect of GTF on glucose incorporation into glycogen in rat hepatocytes was also detected [30].

Another naturally occurring active Cr compound, low-molecular-weight Cr-binding substance (LMWCr), was isolated from mouse or rabbit liver or bovine colostrum [24,31,32]. LMWCr is an anionic mammalian oligopeptide of 1,500 daltons, which binds four chromic ions. Recently, Davis et al. [33] suggested that LMWCr may have a role in the insulin signaling amplification mechanism examined in rat adipocytes.

The purpose of our study was to evaluate the activity of GTF preparations prepared from Brewer’s yeast and the saltbush plant (Atriplex halimus), on glucose metabolism in animal models for both types of diabetes. Yeast cells are the richest known source for GTF. living in (Psamm) which is standard resistant resistant leaves [1:]

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Extract

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for GTF. The saltbush is known traditionally as an antidiabetic plant among the Arabs living in the Negev Desert and near the Dead Sea in Israel. Moreover, the sand rat (Psamomys obesus), which lives in these areas, feeds mainly on the saltbush [34], which supplies most of its nutrients and water. When the Psamomys is fed a standard rodent chow or a high energy diet, it becomes glucose intolerant and insulin resistant; however, its glucose intolerance can be partially corrected by the saltbush leaves [35–38].

**MATERIALS AND METHODS**

**Extract Preparations**

GTF and saltbush preparations were mainly prepared as previously described [25]. Cr was determined by graphite furnace atomic absorption spectrometer. Yeast strain \textit{S. carlsbergensis} cde 176 was used for the experiments. The cells were kept in a solid Cr-depleted medium that contained 6.7g yeast nitrogen base, 20g of glucose, and 18g agar per liter. Cells were grown overnight on a liquid medium without Cr, as previously described [25]. For fermentation experiments, cells were harvested during a stationary phase, washed twice, and resuspended in 0.1 M phosphate buffer pH 5.7. A preparation of $3 \times 10^{7}$ cells/ml was anaerobically incubated at 30°C in Warburg vessels with the additions as specified [25]. CO$_2$ production was measured manometrically.

**Glucose Uptake Experiments**

Glucose uptake experiments were conducted anaerobically at 30°C. Cells were preincubated for 30 minutes with the necessary additives as specified. Addition of tritiated 2 deoxyglucose (2.5 mCi) started the reaction. At each interval, 50 ml were removed, filtered on millipore filter, and washed three times in ice cold water. Radioactive counts were monitored by scintillation spectrometer.

**Animal Experiments**

Sprague Dawley male rats weighing 120–130g were injected intraperitoneally with a single dose of streptozotocin (60 mg/kg bw) in 0.5 ml 0.05 M citrate buffer. Blood glucose levels were measured a week later, and animals with blood glucose levels above 200 mg/dl were chosen for the experiment. Male sand rats (Psamomys obesus) of the Hebrew University Colony were purchased from Harlan Laboratories (Jerusalem). The animals were kept on a high energy diet (Harlan), and sand rats whose blood glucose levels exceeded 200 mg/dl were chosen for the experiment. Spiny mice (Acomys russatus) were obtained from a laboratory breeding colony in the University of Haifa at Oranim. The animals were kept on a high energy diet to make them diabetic.

GTF is stable to proteolytic enzymes [25] and so can be administered orally. GTF preparations were orally administered to diabetic animals by a stomach tube. The oral glucose tolerance test was conducted by loading glucose (2 g/kg bw) and monitoring blood glucose at several intervals. Blood taken from the tail vein was monitored for glucose by a glucometer, One Touch II (Life Scan, CA). Triglycerides were measured using a commercial kit (Sigma). Insulin was purchased from Sigma.
Statistical analysis of the data were performed using a Systat program. Results are expressed as mean ± SEM. Significance was determined by the paired student’s t-test.

RESULTS
Yeast and Saltbush Extracts

The addition of GTF to cells grown on Cr-depleted medium enhanced CO₂ production. Yeast preparations fermenting glucose only (control) showed a linear rate of CO₂ production, whereas addition of GTF to the medium remarkably enhanced the rate of CO₂ formation in the treated cells. There was a high similarity in the effects of GTF derived from different sources. Similar curves were achieved for GTF derived from yeast or from the saltbush plant (Figs. 1 and 2).

There is a dose dependent effect of GTF (as measured by Cr concentrations for both sources), on CO₂ production in yeast cells (Fig. 3). For the saltbush extract, the optimal enhancement of CO₂ production was achieved between 150–250 ng Cr/ml, whereas for the yeast extract preparation, the optimal Cr concentration was between 10–30 ng Cr/ml. At higher Cr concentrations, the rate of enhancement decreased relative to controls in both preparations.

The rate-limiting step in glucose utilization is glucose transport. Following 2-deoxyglucose uptake by yeast cells, there was a fivefold increase in glucose uptake by cells in medium containing GTF compared with the control (Fig. 4).

![Graph showing CO₂ production over time with GTF and control](image_url)

**Fig. 1.** Effect of GTF extracted from yeast on CO₂ production in yeast cells. 3 × 10⁷ cells of S. carlsbergensis ebb 176 in 2.5 ml 0.1 M phosphate buffer pH 5.7 and 15 mM glucose. GTF (5 ng Cr/ml) added.

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**Animal 1**

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Fig. 2. Effect of GTF extracted from the saltbush plant on CO₂ production in yeast cells. 3 x 10⁵ cells of *S. carlsbergensis* club 176 in 2.5 ml 0.1 M phosphate buffer pH 5.7 and 15 mM glucose; GTF (130 ng Cr/ml) added.

**Animal Experiments**

A single dose of GTF (160 ng Cr/animal) was orally administered to streptozotocin-diabetic rats. Blood glucose was monitored for 240 minutes following GTF administration (Fig. 5). An immediate decrease in blood glucose was observed in the treated animals, and the maximal reduction was achieved within 120-180 minutes. Blood glucose levels in untreated diabetic rats remained high.

When the potency of similar doses of both sources of GTF was compared, we found a similar effect on blood glucose reduction: a 22.7% reduction for 280 ng Cr in GTF from yeast, compared with 18.2% reduction for 210 ng Cr in GTF from the saltbush extract.

When different doses of GTF were administered to diabetic rats, dose-dependent values in glucose reduction differed significantly. Whereas 70 ng Cr decreased blood glucose by 10.45%, 280 ng Cr decreased blood glucose by 22.72% (P < 0.05).

Higher reduction in blood glucose could not be achieved by using higher doses of GTF, although higher doses of GTF (1,120 ng Cr/animal) extended the duration of the effect. Blood glucose levels of the treated animals returned to initial values within 6 hours for 280 ng Cr/animal and within 9 hours for 1,120 ng Cr/animal (unpublished results).

There was a correlation between the severity of diabetes and GTF effect. The
reduction effect of GTF on blood glucose in diabetic rats was higher when the degree of diabetes was lower (Table I). For basal glucose values between 220–320 mg/dl, there was a 29.2% decrease following GTF treatment ($P < 0.001$), whereas for severely diabetic rats (blood glucose values between 420–620 mg/dl), the rate of reduction was lower—19.2% ($P < 0.001$).

A correlative decrease in plasma triglyceride levels also was seen in animals supplemented with repeated doses of GTF (100 ng Cr/animal/day) for 30 days (Fig. 6). Whereas triglyceride level in untreated severely diabetic animals reached 263 mg/dl, GTF decreased it to 209 mg/dl. In mildly diabetic rats, GTF decreased the triglyceride level from 155 mg/dl (untreated diabetic control) to 110 mg/dl in the GTF-treated animals.

GTF also reduced elevated glucose levels in type II diabetic animals. Oral glucose tolerance test (OGTT) done on diabetic spiny mice (Fig. 7) showed a remarkable improvement in glucose clearance following administration of GTF. A similar effect was observed in the sand rat. Whereas OGTT in the untreated diabetic rats showed an increase in glucose levels, with the highest level reached about 40 min from loading, the animals treated with GTF showed a remarkable and immediate drop in blood glucose (Fig. 8). There was a 12.75% reduction from control values ($P < 0.01$) in the area under the OGTT curve for animals treated with 35 ng Cr in GTF/animal, and a 15.7% reduction ($P < 0.03$) from control values for animals supplemented with 105 ng Cr in GTF/animal.

We examined the effect of accumulated orally administered doses of GTF on the
ability of diabetic animals to reduce blood glucose levels (Table II). Streptozotocin diabetic rats were daily treated with different doses of GTF. The accumulated doses were 1,000 ng or 3,000 ng Cr/rat. A glucose profile was monitored immediately after the last dose of GTF. As indicated in Table II, reductions in blood glucose levels were higher when a higher dose of GTF had already accumulated in the body.

When a marginal dose of 0.005–0.025 mg/kg of insulin was injected into streptozotocin-diabetic rats, a decrease of 12.5% in blood glucose was observed 2 hours after the injection (Table III). With a single oral dose of GTF, a decrease of 16.75% was observed. A combination of both insulin and GTF created much higher reduction effect in blood glucose (42%), indicating a synergistic effect for insulin and GTF. However, a difference in basal glucose levels between the groups was detected. Whereas both groups started with 102.2 ± 2.91 mg/dl or 102.2 ± 2.98 mg/dl (average value ± SEM) for control and GTF treated animals, respectively, basal glucose levels at the end of the experiment were 98.3 ± 2.75 and 82.3 ± 3.16 for control and treated animals, respectively (P < 0.01).

A toxicity test was conducted on healthy animals (130g body weight) treated with a daily dose of 1,000 ng Cr in GTF (4 times the effective dose) for 4 weeks. No adverse effects were observed in the treated animals when compared to healthy control rats, which were treated daily with equivalent doses of tap water. Body weight, triglyceride levels, and the rate of glucose clearance did not differ between the two groups. In a postmortem dissection, no adverse changes in internal organs (liver, kidney, heart, leg muscles, stomach, spleen, and lungs) could be detected in the treated animals. All these organs were transferred to histological analysis.
Fig. 5. Reduction of blood glucose by GTF in diabetic rats compared to untreated diabetic rats. Fed streptozotocin diabetic rats supplemented orally with a single dose of GTF (160 ng Cr/rat). Glucose levels monitored in blood samples collected from the tail vein.

DISCUSSION

Although Cr has been known for more than 30 years for its essentiality in carbohydrate metabolism [1–4], the exact composition and structure of the glucose tolerance factor (GTF), the natural active Cr compound, are still obscure. There is also no agreement among Cr researchers regarding the characteristics and basic composition of GTF. Our purpose in the present study was to prepare an active extract with GTF activity from two different sources—yeast extract and cells of the saltbush plant (*Atriplex halimus*)—and to examine its activity both in vitro and in vivo.

The material derived from yeast can enhance CO₂ production in yeast cells growing on a Cr-depleted medium; moreover, the material derived from the saltbush can also

<table>
<thead>
<tr>
<th>TABLE I. Effect of Orally Administered Glucose Tolerance Factor (GTF) on Different Levels of Diabetes in Streptozotocin-Diabetic Rats Divided Into Three Groups, According to Basal Glucose Levels</th>
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<tbody>
<tr>
<td>Basal glucose (mg/dl)</td>
</tr>
<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>n</td>
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<tr>
<td>Mean difference* of blood glucose* reduction (%)</td>
</tr>
<tr>
<td>P value</td>
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*Blood glucose measured at time 0 and 2 hours later.

*Difference in reduction rate: Percent of reduction in the presence of GTF minus the percent of reduction in the absence of GTF.
enhance CO2 production in yeast cells. Both extracts showed a dose-dependent effect on yeast cell fermentation. The optimal dose found for yeast extract (10–15 ng Cr/ml) was much lower than that of the saltbush extract (150 ng Cr/ml). This finding may indicate the existence of a dimer or trimer of GTF in saltbush extract, so that much

Fig. 6. Reduction in triglyceride levels by GTF in severely diabetic (350–500 mg/dl) and mildly diabetic (250–350 mg/dl) rats supplemented with repeated doses of GTF (100 ng Cr/day) for 30 days. Each group contained 10 rats.

Fig. 7. Effect of GTF on type II diabetes in diabetic spiny mice (Acomys russatus) supplemented with single dose of GTF (200 ng Cr/animal). Oral glucose tolerance test (OGTT) (2g glucose/kg bw) performed. Glucose clearance compared in the presence and absence of GTF.
Fig. 8. GTF effect in diabetic sand rats (Psammomys obesus) divided according to basal glucose levels into high and low diabetic groups. OGTT performed in the presence and absence of GTF.

Higher concentrations of Cr are needed compared to the yeast preparation. On the animal level, the concentrations of Cr required for both yeast and saltbush preparations are similar, indicating a possible mechanism existing in animal cells that enables them to break the dimer or trimer into monomeric GTF (1 Cr ion per molecule). This assumption demands further investigation.

When the effect of GTF on glucose transport was examined, we found a remarkable enhancement in glucose uptake by yeast cells [28], indicating an insulin-like activity. In our earlier study [39], we demonstrated a high and immediate decrease of blood glucose and free fatty acids levels in type I diabetic rats by intravenous injection of GTF. We also found [25] that the material is stable to proteolytic enzymes and suggested that it could be orally administered. In the present study we orally admin-

<table>
<thead>
<tr>
<th>Accumulated doses of GTF</th>
<th>1,000 ng Cr/rat</th>
<th>3,000 ng Cr/rat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean difference in % reduction in blood glucose* + GTF/no GTF</td>
<td>16.2%</td>
<td>28.3%</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Glucose levels monitored at time 0 and 2 hours after administration of the last dose of GTF.
TABLE III. Blood Glucose Reduction in Diabetic Rats in the Presence or Absence of Marginal Insulin, Measured 2 Hours After Glucose Tolerance Factor (GTF) Administration*  

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% Reduction</th>
<th>Mean difference +GTF/–GTF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No GTF, No insulin</td>
<td>+6.71%</td>
<td>23.5%</td>
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<tr>
<td></td>
<td></td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>GTF</td>
<td>–16.75%</td>
<td></td>
</tr>
<tr>
<td>Insulin*</td>
<td>–12.5%</td>
<td>29.5%</td>
</tr>
<tr>
<td>Insulin* + GTF</td>
<td>–2%</td>
<td></td>
</tr>
</tbody>
</table>

*Results represent average values for different doses of GTF.  
*Marginal dose: 0.005–0.025 mg/kg.

istered GTF to diabetic animals and found an immediate reduction in blood glucose in the treated animals. The advantages of oral administration are evident, bearing in mind the difficulties associated with insulin administration. The reduction rate is similar for both preparations of GTF, indicating that the same material (i.e., GTF) is being extracted.

Of several known sources for GTF [3,4,20,22,25], yeast cells are one of the richest. We have shown that both the saltbush and yeast cells are rich sources for GTF. Moreover, our data indicate that GTF, extracted from saltbush, has high antidiabetic activity on elevated levels of blood glucose in the sand rat. By that, one can deduce that the antidiabetic action of the saltbush plant is based on the existence of GTF in its leaves.

The effect exhibited by GTF on blood glucose reduction in both types of diabetic animals was immediate and statistically significant. However, the rate of glucose reduction depends on the severity of diabetes and the dose of GTF administered. It is important to note that although the maximal reduction effect on blood glucose in type I diabetic rats was achieved by a dose of 280–560 ng Cr/rat, the duration of the effect was much longer when the dose was increased.

The long-term effect of GTF on blood glucose and triglyceride concentrations shows a possible accumulation of the material in the body. Moreover, we also found a reduction in basal glucose in several type I diabetic rats after repeated doses of GTF (unpublished data). We can assume that GTF might accumulate in internal pools in the body, and when the body pools become saturated, the influence of GTF on carbohydrate metabolism is optimal.

Summarizing our results with the effect of GTF (derived from two different sources) on glucose metabolism in vivo and in vitro, we may propose an insulin-like effect of GTF at the cellular level. Simple Cr salts have only a partial influence on improving glucose tolerance [40–43], need high concentrations of Cr (up to 60 mg Cr/day), and a long period for treatment (several months). It is known that simple Cr salts are poorly absorbed and tend to polymerize in physiologic pH [2]. These findings can explain the limited effects of Cr salts on improving glucose tolerance and lipid metabolism in animals and human subjects. Organic Cr compounds are easily absorbed by the body [14,16]. Among the organic Cr compounds widely used in the last few years, Cr picolinate (CrPic) is most successful. Although this compound is well
absorbed in the body, its beneficial effects appear only after several weeks of treatment [44-49].

GTF preparations exhibit a high, immediate, and statistically significant influence on glucose and lipid metabolism, as shown in the present study and in our previous work [39]. We can assume that the body absorbs inorganic or organic Cr compounds from the diet and coverts them to active GTF. In cases of low Cr conditions or in diabetes, when the body might lose the ability to synthesize GTF from simple Cr compounds, the effect of administered GTF is remarkable.

Our in vivo studies also support the in vitro findings: GTF exhibits insulin-like effects on both types of diabetic animals by decreasing their blood glucose and lipids. We demonstrated a synergism between GTF and insulin effects on Type I diabetic rats. Similar findings indicating a synergism between Cr compounds and insulin have been reported in the literature. Cefalu et al. [50] reported a highly significant effect of supplemental Cr as CrPic on the insulin sensitivity of glucose intolerant subjects. Stoffler et al. [51,52] demonstrated that Cr supplementation is needed for preservation of normal insulin sensitivity in peripheral tissues (which are impaired with the depletion of Cr), in addition to a modulatory role in maintenance of normal beta-cell sensitivity.

The exact mechanism of action of GTF (or Cr compounds) on insulin function is not known. Several mechanisms have been postulated, beginning with a direct binding of Cr to insulin [3], increased binding of insulin to red blood cells [53], increased sensitivity of myoblasts to insulin by the addition of Cr [54], and increased insulin internalization in cultured rat skeletal muscle cells by addition of Cr [55]. Cr also appears to alter the dephosphorylation of insulin receptor proteins. Preliminary results from our laboratory indicate a possible inhibitory effect of GTF on phosphorysinephosphate activity. Our findings are in concert with those presented by Davis et al. [33]. These researchers showed that LMWCr (a mammalian oligopeptide that binds 4 chromic ions) can potentiate insulin action by increasing the formation of lipids and CO₂ from glucose by isolated adipocytes. They found that LMWCr stimulates the activity of the insulin receptor protein tyrosine kinase in the presence of insulin. Although LMWCr differs from what is known about the GTF, it is an organic Cr compound derived from natural sources and exhibits similar activity on the cellular level.

There is a great need to investigate further the natural organic Cr compounds and to discover the composition and structure of the Cr binding factor, or factors, which are essential for normal carbohydrate metabolism.

REFERENCES

1. \( \text{Cr} \) treatment in diabetic rats increases insulin sensitivity and reduces blood glucose levels.

2. Chromium deficiency is linked to type 2 diabetes and metabolic syndrome, with beneficial effects observed when chromium supplementation is administered.

3. Chromium play a role in the regulation of insulin secretion and glucose metabolism.

4. Incretin hormones, such as GLP-1 and GIP, are implicated in the improved glucose control seen with chromium supplementation.

5. Chromium enhances the action of insulin by increasing insulin receptor expression.

6. Chromium supplementation has been shown to improve glycemic control in individuals with type 2 diabetes and prediabetes.

7. Additional studies are needed to fully understand the mechanisms by which chromium improves insulin sensitivity and glycemic control.